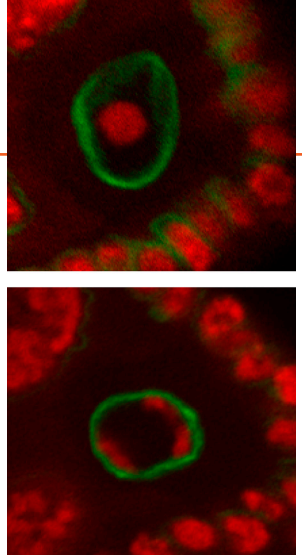


Oocyte DNA (red) forms a compact karyosome before meiosis (top). In flies that have a mutant NHK-1, the DNA remains near the nuclear envelope (bottom).

Text by Nicole LeBrasseur
lebrasn@rockefeller.edu

Chromosomes leave envelope for karyosome

In the large volume of an oocyte, chromosomes huddle together before the meiotic spindle forms. Fashioning this huddled mass—called a karyosome—requires that chromosomes first be released from the nuclear envelope, according to results from Lancaster et al.

Because oocytes lack centrosomes, they assemble spindle microtubules from chromatin. By clustering chromosomes together, karyosomes help make sure that only one spindle is generated. Karyosomes don't form in fly oocytes that lack a kinase called NHK-1. In the new work, the authors found that chromosomes in *nhk-1* mutant cells made widespread contacts with the nuclear envelope, whereas in normal cells, the karyosome formed away from the envelope.

The group found that an NHK-1 substrate from fly cells was an envelope-associated protein called BAF. In their model, BAF hooks chromatin to the nuclear envelope during DNA recombination. But phosphorylated BAF unfastened the connection and freed chromosomes to crowd together. Expression of a BAF mutant that could not be phosphorylated maintained a link between the DNA and an inner nuclear envelope protein called Otefin.

The group is now determining whether NHK1, which is itself phosphorylated late in meiosis, might be activated by cell cycle–regulated kinases. The mammalian versions of BAF and NHK-1 are needed for structural changes in the nuclear envelope during mitosis, but no one has yet looked at their role in meiosis. JCB

Reference: Lancaster, O.M., et al. 2007. *J. Cell Biol.* 179:817–824.

Slow-moving Alzheimer's

Traffic delays might do more than make you late to work. Findings from Kim et al. now suggest that slowed trafficking of the γ-secretase protease might cause Alzheimer's disease.

γ-Secretase is a multisubunit complex that includes presenilin. Mutations in presenilin are associated with inherited forms of Alzheimer's. Scientists do not yet understand how these varied mutations—which can fall at multiple points along the protein—all lead to the misprocessing of the amyloid precursor protein to create an aggregation-prone form of Aβ.

Presenilin is assembled with the rest of the γ-secretase complex within the secretory pathway. In the new report, the team found that trafficking through at least part of this pathway—out of the ER and into COPII vesicles—was slowed by presenilin mutations that cause Alzheimer's. Packaging of the mutants into COPII vesicles was reduced in in vitro ER budding assays.

Exit from the ER is often delayed by protein misfolding, which is a problem that affects many mutant versions of presenilin. Helping the sluggish mutants fold by treatment with a chemical chaperone restored their packaging into vesicles.

Retention of the mutants within the ER probably does not itself create the faulty Aβ, as the authors found only inactive γ-secretase in both the ER and COPII vesicles. The protease must therefore be processed and activated in a downstream compartment such as the Golgi. If folding-challenged presenilin mutants are also delayed when they exit this later compartment, prolonged exposure to processing enzymes might create their distorted cleavage properties. JCB

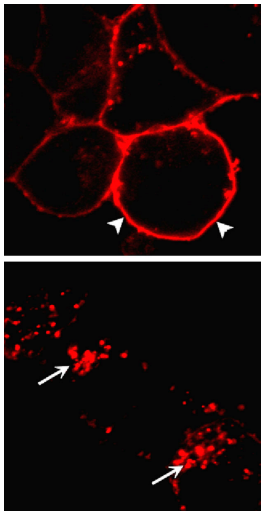
Reference: Kim, J., et al. 2007. *J. Cell Biol.* 179:951–963.

Peptidase frees receptors in endosomes

Internalized pain receptors are freed up by a peptidase for another round of agony, Padilla et al. reveal.

Peptidases on the cell surface cleave and thereby activate or inactivate small, extracellular peptides such as angiotensin. The enzymes also reside in internal compartments called endosomes, where their action is less apparent.

The new work shows that a peptidase called ECE-1 needs the low pH of the endosome to cleave several of its targets. One such peptide target was CGRP, which is released by cells during inflammation. Binding of CGRP to its receptor, CLR, induces pain signaling pathways in neurons. The peptide–receptor complex is then internalized into endosomes, which switches off the pain pathway.



The recycling (top, arrowheads) of CLR (red) back to the plasma membrane is blocked in cells lacking ECE-1 (bottom).

Padilla and colleagues found that the internalized peptide/receptor was accompanied by ECE-1 into endosomes. There, the low pH encouraged the peptide to fall off its receptor. Cleavage by ECE-1 helped to ensure that the peptide did not rebind.

The dissolution of the pair released an associated scaffolding protein called β-arrestin, whose liberation allowed the receptor to return to the cell surface. This ECE-1–induced recycling was necessary for cells to respond to a second round of CGRP. Inhibitors of ECE-1, which were developed to block activation of a peptide that raises blood pressure, might thus have analgesic and antiinflammatory effects. JCB

Reference: Padilla, B.E., et al. 2007. *J. Cell Biol.* 179:981–997.